Exhibit D

RECEIVED

FEB 04 2002

TECH CENTER 1600/2900

PATENT
Customer No. 22,852
Attorney Docket No. 0[illegible]0013

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#4

02 JAN 31 PM 12:13

In re Application of:	
Michael SCAIFE et al.	
Appln. No.: 09/998,206	Group Art Unit: 1614
Filed: December 3, 2001	Examiner: R. Henley III
For: METHOD FOR INCREASING THE BIOAVAILABILITY OF METAXALONE	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PETITION TO MAKE SPECIAL
UNDER M.P.E.P. § 708.02(VIII)

Applicants petition the Commissioner of Patents and Trademarks under 37 C.F.R. § 1.102 and M.P.E.P. § 708.02(VIII) to make this application special and receive accelerated examination. In accordance with M.P.E.P. § 708.02(VIII), Applicants are enclosing a check for $130.00 to cover the fee for this Petition as set forth in 37 C.F.R. § 1.17(i). If any additional fee is required in connection with the filing of this Petition, please charge that fee to our Deposit Account No. 06-0916.

All claims presented for examination are directed to a single invention. If the Patent Office determines that all of the claims are not obviously directed to a single invention, Applicants will make, without traverse, an election of claims for prosecution in the

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

01/31/2002 RHARRON 00000088 09998206

01 FC:122 130.00 OP

I. Preexamination Search

In accordance with M.P.E.P. § 708.02(VIII), a preexamination search was conducted in connection with the claimed method of increasing the bioavailability of metaxalone by administering a therapeutically effective amount of metaxalone in a pharmaceutical composition with food. The field of this search included U.S. patents in class 514, subclasses 161, 384, 457, 458 and 558, and class 424, subclasses 464, 468, 469 and 484. In addition, a computer search was conducted in the Claims data base of the Dialog Information System using the key terms "metaxalone" and food."

The following references located by the search were determined to be most closely related to the subject matter of the pending claims:

(1) U.S. Patent No. 3,993,767 to Alphin et al.;

(2) U.S. Patent No. 4,036,957 to Alphin et al.;

(3) U.S. Patent No. 4,792,449 to Ausman et al.;

(4) U.S. Patent No. 4,820,690 to Gregory et al.;

(5) U.S. Patent No. 5,840,688 to Tso;

(6) U.S. Patent No. 5,977,175 to Lin;

(7) U.S. Patent No. 5,989,583 to Amselem;

(8) U.S. Patent No. 6,099,859 to Cheng et al.;

(9) U.S. Patent No. 6,143,325 to Dennis et al.; and

(10) U.S. Patent Application Publication No. 2001/0024659 A1 to Chen et al.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

A copy of each of the foregoing references is provided with an Information Disclosure Statement and a Form PTO-1449 filed concurrently with this Petition. The identification of a reference in this Petition should not be construed as an admission that the reference is prior art to the claims of the present application.

II. Independent Claims of the Present Invention

1. A method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

9. A method of increasing the rate and extent of absorption of an oral dosage form of metaxalone as measured by the drug concentration attained in the blood stream over time in a patient in need of a therapeutic effect thereof comprising, administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

17. An item of manufacture comprising a container containing a pharmaceutical composition of metaxalone, wherein the container is associated with printed labeling advising that taking the composition with food increases the bioavailability of metaxalone to a patient receiving the composition by oral administration.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

III. Detailed Description of the References

None of the above references discloses or suggests a method of increasing the oral bioavailability of metaxalone to a patient by administering a therapeutically effective

amount of metaxalone in a pharmaceutical composition with food, as claimed by Applicants. Applicants' specific comments concerning the references are set forth below:

A. U.S. Patent No. 3,993,767

This patent discloses methods of treating symptomatic conditions of inflammation due to chronic and acute rheumatic and degenerative joint disease with a combination of indomethacin or phenylbutazone and a phenoxymethyl-2-oxazolidinone, resulting in beneficial reduction in side effects of ulceration and bleeding in the lower intestinal tract.

Metaxalone is said to represent a preferred embodiment of Formula I of the patent. Col. 4, lines 23-25. The patent also describes the preparation, for veterinary use, of a combination of indomethacin or phenylbutazone and phenoxymethyl-2-oxazolidinones of Formula I in tablets and capsules for unit dosage form of administration or in the form of powders and granules for admixing with food. Col. 12, lines 25-53. There is no teaching or suggestion of Applicants' discovery that the oral bioavailability of metaxalone to a patient may be increased by administering it in a pharmaceutical composition with food.

B. U.S. Patent No. 4,036,957

This patent describes pharmaceutical methods, combinations and compositions for reducing gastric bleeding during aspirin therapy for inflammation. Compounds used in combination with aspirin include phenoxy- and substituted-phenoxy alcohols, carbamates, aminoalcohols, carbamoylalcohols, oxazolidinones, pyrrolidines,

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

thiosemicarbazides and aminoalkylacetamides. The compounds act systemically to ameliorate gastric bleeding otherwise caused by aspirin. Compound 15 within the disclosed Formula I is metaxalone.

The patent further describes the preparation, for veterinary use, of a combination of aspirin and phenoxy compounds of Formula I in tablets and capsules for unit dosage form of administration or in the form of powders and granules for admixing with food. Col. 13, lines 19-43. There is no teaching or suggestion that the oral bioavailability of metaxalone to a patient may be increased by administering it in a pharmaceutical composition with food.

C. U.S. Patent No. 4,792,449

This patent discloses a method for administering drugs in which a lipophilic drug is solubilized by a food, such as chocolate, and admixed with an oil-based carrier. The lipid soluble drug is said to be conveyed to the gastrointestinal tract and absorbed as intended, without day-to-day variations in dose. The patent teaches that the invention can be used with any drug which can be incorporated into an oil base carrier. Col. 2, lines 23-24. There is no disclosure or suggestion of Applicants' discovery that the oral bioavailability of metaxalone to a patient may be increased by administering it in a pharmaceutical composition with food.

D. U.S. Patent No. 4,820,690

This patent discloses pharmaceutical compositions for oral administration comprising human urogastrone or a urogastrone fragment as an active ingredient. The

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

patent teaches that the compositions may be administered one to four times, and preferably once, per day and preferably may be administered before food, for example about an hour before food. Col. 4, lines 2-5. There is no teaching or suggestion of increasing the oral bioavailability of metaxalone to a patient by administering it with food, as claimed by Applicants.

E. U.S. Patent No. 5,840,688

This patent describes peptides corresponding to specific portions of the apolipoprotein A-IV (apo A-IV). The peptides have eating suppressant properties when administered centrally or peripherally and may be used in compositions and methods for suppressing the appetite and controlling food intake.

The patent further teaches that the peptides may be formulated into food compositions such as "nutriceuticals," which are defined as any foodstuff such as, for example, liquid or powder compositions that have a pharmaceutical effect when consumed (i.e., appetite suppression or inhibition of food intake). Col. 7, lines 32-37. The peptides may be added, admixed, blended or otherwise incorporated with or into powders, liquids (such as shakes), gels, gums, snackfoods, cakes, candies or other comestibles for use as food compositions or food supplements that suppress appetite or inhibit food intake. Col. 7, lines 38-43. There is no teaching or suggestion of increasing the oral bioavailability of metaxalone to a patient by administering it in a pharmaceutical composition with food.

F. U.S. Patent No. 5,977,175

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

This patent describes methods and compositions for slowing gastrointestinal transit and prolonging residence time to optimize presentation and absorption of ingested nutrients and/or pharmacologically active agents in the small intestine to prevent and/or reduce ineffectiveness thereof due to malabsorption. The patent further describes methods and compositions for enhancing the bioavailability and therapeutic effectiveness of pharmacologically active agents.

The patent teaches that, in order to stretch biologic activity so that one has a convenient daily dosage regimen, the compositions may be administered prior to ingestion of a food, nutrient and/or pharmacologically active agent, preferably up to 24 hours prior to such ingestion. Col. 7, lines 27-35. There is no teaching or suggestion that the oral bioavailability of metaxalone to a patient may be increased by administering it with food.

G. U.S. Patent No. 5,989,583

This patent discloses lipophilic substances of poor oral bioavailability mixed with at least one solid fat and phospholipid to obtain a dried solid composition suitable as an oral dosage form. The solid lipid compositions may be used with food additives or dietary supplements such as Coenzyme Q10 and for pharmaceuticals such as dexanabinol. The Coenzyme Q10-dry lipid mixtures and dexanabinol-dry lipid mixtures are said to show improved drug release in vitro and enhanced oral bioavailability in vivo compared to known formulations. There is no teaching or suggestion of increasing the oral bioavailability of metaxalone to a patient by administering it with food.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

H. U.S. Patent No. 6,099,859

This patent discloses a controlled release antihyperglycemic tablet that does not contain an expanding polymer, which comprises a core containing the antihyperglycemic drug, a semipermeable membrane coating the core and at least one passageway in the membrane.

The patent teaches that the disclosed dosage form can provide therapeutic levels of the antihyperglycemic drug for 12- to 24-hour periods without a decrease in bioavailability if taken with food or with a slight increase in the bioavailability of the antihyperglycemic drug when the controlled release dosage form is administered with food. Col. 2, lines 44-50. In a preferred embodiment, the dosage form is administered once a day, ideally with or after a meal and most preferably with or after the evening meal, and provides therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 8-12 hours after administration. Col. 2, lines 50-55; FIG. 7; FIG. 8; col. 9, lines 22-52. There is no teaching or suggestion of Applicants' invention directed to increasing the oral bioavailability of metaxalone to a patient by administering it in a pharmaceutical composition with food.

I. U.S. Patent No. 6,143,325

This patent discloses extended-release nefazodone compositions containing nefazodone hydrochloride, ionic and non-ionic gelling polymers, an insoluble hydrophilic agent, and optional pharmaceutically acceptable excipients. These compositions are formulated into unit dosage forms for improved oral administration. The improvements

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

are said to comprise an extended drug release profile providing comparative levels of nefazodone with respect to immediate release dosage forms and, additionally, demonstrating the lack of a food effect.

The patent further describes a comparative pharmacokinetic study in fed and fasted subjects using the disclosed nefazodone ER formulation of Example 1. The study is said to show an unexpected lack of a food effect in contrast to a conventional controlled-release nefazodone formulation. Col. 8, lines 25-67. There is no teaching or suggestion that the oral bioavailability of metaxalone to a patient may be increased by administering it with food.

J. U.S. Patent Application Publication No. 2001/0024659 A1

This patent application discloses sustained release pharmaceutical formulations comprising an antihyperglycemic drug or a pharmaceutically acceptable salt thereof. The application teaches that the disclosed formulation can provide therapeutic levels of the antihyperglycemic drug for 12- to 24-hour periods without a decrease in bioavailability if taken with food or with a slight increase in the bioavailability of the antihyperglycemic drug when the controlled release dosage form is administered with food. Pages 1-2, paragraph 0021. In a preferred embodiment, the formulation is administered once a day, ideally with or after a meal and most preferably with or after the evening meal, and provides therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 8-12 hours after administration. Page 2, paragraph 0021; page 5, paragraphs 0080-0081. There is no teaching or suggestion of

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

increasing the oral bioavailability of metaxalone to a patient by administering it with food.

In summary, for these reasons, none of the references discussed above discloses or suggests the claimed method of increasing the oral bioavailability of metaxalone to a patient by administering a therapeutically effective amount of metaxalone in a pharmaceutical composition with food. No reference or combination of references describes or suggests Applicants' important discovery that the oral bioavailability of metaxalone to a patient can be significantly improved by administering it with food. The claims are therefore patentable over these references.

IV. Documents Referenced in the Specification

The documents below are referenced in the specification. None discloses or suggests a method of increasing the oral bioavailability of metaxalone to a patient by administering a therapeutically effective amount of metaxalone in a pharmaceutical composition with food, as claimed by Applicants.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

A. The Merck Index (1989)

This document, referenced on page 1 of the specification, discloses the structure of metaxalone and identifies it as a skeletal muscle relaxant. This document does not contain any description of any possible side effects of metaxalone or its mode of administration.

B. Lunnsford et al., "5-Aryloxymethyl-2-oxazolidinones," Journal of the American Chemical Society, 82, pg. 1166 (1960)

This document, referenced at page 2 of the specification, discloses metaxalone, its method of manufacture and that it has been investigated for use as a skeletal muscle relaxant. This document does not contain any description of any possible side effects of metaxalone or its mode of administration.

C. U.S. Patent No. 3,062,827

This document, referenced at page 2 of the specification, discloses metaxalone, its method of manufacture and its use as an interneuronal blocking agent or depressant of central synaptic transmission. This document does not contain any description of any possible side effects of metaxalone or its mode of administration.

D. Skelaxin®, 2001 Physicians' Desk Reference (2001)

This document, referenced at page 2 of the specification, contains a description of the commercial product Skelaxin® (metaxalone). Metaxalone is indicated as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The recommended dose is

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

two tablets (800 mg) three to four times a day. There is no disclosure that the oral bioavailability of metaxalone to a patient can be significantly improved by administering it with food.

V. Conclusion

Applicants submit that the requirements of M.P.E.P. § 708.02(VIII) have been met. In addition, the pending claims are allowable over the above references considered either individually or in any reasonable combination.

Accordingly, Applicants respectfully request that the Patent Office grant this Petition and allow the claims of this application.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Charles E Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: January 31, 2002

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com